accord with physiologic requirements. These are called dual-chamber rate-modulated systems and are identified by the code DDDR. The increased complexity of these systems has led to difficulty interpreting electrocardiographic rhythms, an increased requirement for follow-up, and increased cost. Given these factors, it must be asked if these technologic advances are worth the additional costs. Because it is expected that a pacemaker will function properly for five to ten years, the long-term consequences of a pacing mode need to be considered when evaluating the cost.

Recent studies have shown that the maintenance of atrioventricular synchrony is associated with a dramatic reduction in the incidence of atrial fibrillation, systemic emboli, the development of overt congestive heart failure, and even mortality. In addition, adverse hemodynamic consequences of single-chamber (code VVI) pacing, originally thought to have an incidence of only 10% to 15%, are now being found in more than 80% of VVI-paced patients. The lower number reflects severe manifestations of the pacemaker syndrome that include overt congestive heart failure and syncope. The higher number identifies symptoms for which the body can compensate or with which the patient can learn to live but nevertheless affect the quality of life. These include palpitations caused by canon A waves resulting from the atrium contracting against a closed atrioventricular valve, increased mitral and tricuspid regurgitation, a nonproductive cough, symptoms of low cardiac output, and decreased cerebral perfusion resulting in an unsteady gait and periods of increased confusion. These symptoms may be intermittent.

The goal of treating a cardiac rhythm abnormality is to restore normal sinus rhythm. Sinus rhythm supports the heart rate at rest and accelerates with exercise while at all times maintaining synchrony between the atrium and ventricles. Dual-chamber rate-modulated pacing is the closest that technologic advances have come to mimicking normal sinus rhythm. Despite the increased costs associated with implanting the device, studies are documenting both the short- and long-term benefits of dual-chamber pacing. If the costs associated with repeated hospital admissions are considered—increased medication requirements and the quality of life associated with the late consequences of single-chamber pacing—dual-chamber pacing improves a patient's quality of life and becomes more cost effective. Several studies have shown that there is no longer justification to implant a single-chamber pacemaker in every patient who requires pacing therapy. The American College of Cardiology and American Heart Association guidelines state that

> long-term absence of atrioventricular synchrony increases the incidence of atrial fibrillation and stroke and may reduce patient life expectancy. . . . therefore, the concept that the single chamber pacemaker with adaptive-rate functions is equivalent to the dual chamber pacemaker cannot be supported.

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Diabetic Nephropathy Revisited

DIABETIC NEPHROPATHY is the leading cause of end-stage renal disease in patients with diabetes mellitus and is the single most frequent reason in the United States for starting long-term hemodialysis treatment. Diabetic nephropathy is defined by persistent proteinuria on a dipstick test (or greater than 0.3 grams per day urinary albumin excretion) in the absence of other renal disease. The prevalence of end-stage renal disease caused by diabetes ranges from less than 10% in patients with type II diabetes to about 40% in those with type I diabetes. Nonetheless, some groups with type II diabetes—such as African Americans, Asian Americans, Hispanic Americans, and Native Americans—have a much higher risk of end-stage renal disease than expected. Furthermore, diabetic patients with a family history of diabetic nephropathy or hypertension are at increased risk of nephropathy developing.

Therapeutic and preventive measures both aim at delaying the progression of diabetic nephropathy to end-stage renal disease. The control of hyperglycemia to "near normal" (tight control) is often considered an important first step in attempting to slow the progression of microalbuminuria to renal failure. Some renal mesangial changes regress with tight control and pancreatic transplantation. Although debate continues about the merits of tight control, poor glycemic control does strongly predict clinical diabetic nephropathy in diabetes. Once nephropathy is established, the control of blood glucose is ineffective in reversing the process.

Blood pressure control in patients with diabetes dramatically reduces the albumin excretion rate and slows the progression of renal failure. A loss of renal mass, as can occur in diabetic patients, results in compensatory glomerular hyperfiltration in the remaining nephrons. Although angiotensin-converting enzyme (ACE) inhibitors and some calcium channel blockers reduce the glomerular hyperfiltration, ACE inhibitors may worsen renal function and induce or worsen hyperkalemia in some patients.

Protein-restricted diets show promise in decreasing glomerular hyperfiltration and may play a role in therapy and prevention. Some studies show that such diets can decrease the urinary albumin content and delay the decline of creatinine clearance. Whether this results in the prevention of clinical renal failure over the long term remains controversial.

Other interventions proposed to slow the rate of progression of chronic renal failure in diabetic patients include platelet (thromboxane synthesis) inhibitors; phosphate-restricted, low-protein diets; vegetarian (no animal protein) diets; and aldose reductase inhibitors. The role of these interventions should be clarified in this decade.

In summary, diabetic nephropathy is a serious and costly problem. End-stage renal disease does not develop in all diabetic patients; why it does in some and not others is an enigma. Some preventive strategies are well established, and the aggressive control of even mild hypertension is essential. The increasingly diversified group of proteinuria-sparing drugs makes it easier to individualize care. It is prudent to maintain tight glycemic control, especially in patients with type I diabetes and in high-risk subpopulations of those with type II diabetes. A cautious use of any potentially nephrotoxic medication or intravenously administered contrast media is warranted. Protein restriction is highly advisable. Screening for proteinuria is recommended because it may

stimulate both physician and patient to be more diligent in their preventive regimen. Prevention is certainly better than cure, because no cure for established diabetic nephropathy is in sight.

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Treatment of Chronic Hepatitis C With Recombinant Interferon Alfa

NATURAL ALPHA INTERFERONS are host-derived proteins produced mainly by monocytes and B lymphocytes in response to viral and other stimuli. Because of its antiviral, antiproliferative, and immunomodulatory effects, interferon (IFN) has been used in the treatment of hairy cell leukemia, condylomata acuminata, and Kaposi's sarcoma associated with the acquired immunodeficiency syndrome. Advances in recombinant DNA technology have allowed the production of interferon alfa (IFN-α) in large quantities for clinical use. The Food and Drug Administration has recently added chronic non-A, non-B hepatitis (hepatitis C) to the list of approved indications for treatment with recombinant IFN-α2b.

Hepatitis C is responsible for more than 90% of cases of post-transfusional hepatitis and nearly half of the cases of sporadic hepatitis. About half of the cases of acute hepatitis C will lead to chronic hepatitis, and cirrhosis will develop in 20% of this group. In randomized, controlled clinical trials, 50% of patients with parenterally acquired chronic hepatitis C showed substantial improvement in serum alanine aminotransferase (ALT) levels when recombinant IFN-α2b was administered subcutaneously at a dose of 3 million international units three times a week for six months. This compared favorably with the 5% to 10% per year spontaneous remission rate in untreated patients. Of those responding to IFN-α2b treatment, 70% achieved reductions of ALT to normal levels. Relapse rates approached 50% within six months after the completion of therapy regardless of the dosage used. Retreatment with the initial dose regimen achieved a prompt remission in most patients. Transient elevations of serum ALT levels may occur in some patients after therapy is discontinued, but this by itself is not considered an indication for retreatment. Improvement determined histologically, primarily regression of lobular and periportal inflammation, was also observed in some patients. The presence of the neutralizing antibody to IFN, detected in the serum of some treated patients, did not have a demonstrable effect on the course of the disease or the response to therapy in the short term.

The most frequent side effects of IFN-α2b therapy are flulike symptoms (myalgia, headache, fever) that typically resolve after the first few doses. Other adverse reactions include diarrhea, alopecia, rash, altered mental state, depression, cytopenia, and deranged thyroid function. Reducing the dose temporarily usually ameliorates these symptoms. Current criteria for exclusion from IFN-α2b therapy include decompensated liver disease, cytopenia, other (nonviral) causes of liver disease, serious concurrent medical illness, pregnancy, the presence of antibodies to the human immunodeficiency virus, a previous organ transplant, renal failure, a history of neuropsychiatric problems, autoimmune disorders, and preexisting thyroid abnormalities if thyroid function cannot be maintained in the normal range by medication.

The effect of IFN-α2b therapy on viral replication, infectivity, and the long-term natural history of chronic hepatitis is not known. Current studies will show if higher doses or a longer duration of treatment with IFN-α2b will increase the frequency and duration of remission.

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Transesophageal Echocardiography

TRANSESOPHAGEAL ECHOCARDIOGRAPHY (TEE) has become an accepted clinical procedure and is considered a logical extension of a complete echocardiographic examination in selected patients. Access to the heart in almost all patients, safety, patient tolerance, and predictably high-quality images have fostered a wide application. Transesophageal echocardiography allows the evaluation of cardiac, valvular, and vascular structures and function in a relatively noninvasive manner. Imaging of the heart through the esophagus provides an unobstructed view of cardiac structures and the great vessels and allows the use of higher frequency transducers, which results in better image quality.

Transesophageal echocardiography examinations are done with an ultrasound transducer mounted at the tip of a modified gastroscope. It can be done in an echocardiography laboratory, in an emergency department, on regular wards, in intensive care units, and in an operating room. In conscious patients, the fasting time before the TEE study should be at least three to six hours. Endocarditis prophylaxis is applied to high-risk patients, especially those with prosthetic valves. Anticoagulation is no longer a contraindication. Patients are generally premedicated, especially those who are apprehensive. A regimen used in our laboratory is 1 to 2 mg of midazolam hydrochloride given intravenously. The posterior pharynx of each patient is anesthetized topically with a 14% benzocaine spray before the procedure.

Conventional transesophageal endoscopes allow imaging in the horizontal plane. Specific limitations of horizontal imaging include difficulty in visualizing extreme anterior and posterior structures and an inability to depict contiguous long-axis or off-axis spatial relationships. Because the heart is a complex organ with three-dimensional relationships and interrelated structures, the ideal tomographic imaging technology should delineate all three anatomic planes. Biplanar imaging has recently become available, adding an orthogonal longitudinal plane and thus enhancing the diagnostic poten-